



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA XX-XXX
NDA XX-XXX

Sponsor Company
Attention: Contact
Title and address

Dear Dr. *Contact*:

To obtain needed pediatric information on *ampicillin* for the treatment of *neonatal sepsis and/or meningitis*, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. As used in this Written Request, neonate refers to the first 28 days of life.

Introduction:

Neonates are at risk for serious bacterial infections which include meningitis, bacteremia, sepsis and urinary tract infections. Most of these children are admitted to the hospital where they receive antibiotics¹. Early onset of bacterial infection (< 7 days of life) reflects vertical transmission, usually caused by group B *Streptococcus* (GBS), *Escherichia coli*, *Listeria monocytogenes*, or *Enterococcus* species, and is a significant cause of illness and death among low birth weight infants². Late onset infections suggest nosocomial, community-acquired infections or late onset GBS; these may be caused by gram-negative organisms as well as staphylococcal species. The first line of antibiotic therapy is ampicillin in combination with gentamicin or a third generation cephalosporin.

Recommendations for initial antibiotic coverage were developed when GBS infections were predominant and antibiotic resistance was rare. Despite recent reports of ampicillin resistance, as well as changes in the epidemiology of bacterial infections^{3, 4, 5}, ampicillin in combination with an aminoglycoside or a third generation cephalosporin remains the mainstay of therapy for the treatment of neonates with suspected sepsis and/or meningitis⁶. The rationale for combining a penicillin-class agent with an aminoglycoside is based on evidence from *in vitro* and animal studies that suggests improved activity with the combination over the penicillin alone^{7, 8}. There are no clinical trials to formally support this practice. Because of the increasing incidence of ampicillin resistance and the decreasing incidence of infections by *L. monocytogenes*, therapy with a third-generation cephalosporin with or without gentamicin may be an alternative^{3, 4}.

Ampicillin was approved by the FDA in 1965. It is labeled for pediatric use for the treatment of respiratory tract and soft tissue infections, gastrointestinal and genitourinary tract infections, bacterial meningitis, and septicemia. However, there is no specified dosage for the neonatal group. The currently approved dosage and administration from the ampicillin label for the indication of bacterial meningitis and septicemia are as follows (excerpted from the ampicillin label, Marsam Pharmaceuticals Inc., July 1995):

“Bacterial Meningitis

Adults and children- 150 to 200 mg/kg/day in equally divided doses every 3 to 4 hours. (Treatment may be initiated with intravenous infusion therapy and continued with intramuscular injections.) The doses for other infections may be given by either the intravenous or intramuscular route.

“Septicemia

Adults and Children- 150 to 200 mg/kg/day. Start with intravenous administration for at least 3 days and continue with the intramuscular route every 3 to 4 hours.

“Treatment of all infections should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. A minimum of 10 days treatment is recommended for any infection caused by Group A beta-hemolytic streptococci to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.”

The dosage specified in the label differs from the dosing regimen recommended by the American Academy of Pediatrics (AAP). The dosing regimens currently recommended by the AAP and used in clinical practice are as follows (excerpted from the 2003 Red Book):

“...Ampicillin plus an aminoglycoside is the initial treatment of choice for a newborn infant with presumptive invasive GBS infection. ...For ampicillin, the recommended dosage for infants with meningitis 7 days of age or younger is 200 to 300 mg/kg/day, intravenously, in 3 divided doses; for infants older than 7 days of age, 300 mg/kg per day, intravenously, in 4 to 6 divided doses is recommended.”⁹

“...Ampicillin – Route IV or IM;

- Infants 0-4w of age, BW <1200 g, 25-50 mg/kg every 12 h
- Infants <1w of age, BW 1200-2000 g, 25-50 mg/kg every 12 h; BW >2000 g, 25-50 mg/kg every 8 h
- Infants ≥1w of age, BW 1200-2000 g, 25-50 mg/kg every 8 h; BW >2000 g, 25-50 mg/kg every 6 h”

“For meningitis, the larger dosage is recommended. Some experts recommend even larger dosages for group B streptococcal meningitis.”¹⁰

Infant maturity as reflected by gestational and chronological ages needs to be considered in relation to dosage amount and interval. Physiologic factors such as absorption, distribution, metabolism, and excretion are constantly changing during the neonatal period. Other factors that influence the pharmacokinetics in the neonatal period include: drug biotransformation,

extracellular fluid volume, protein binding, renal immaturity and immaturity of enzyme systems¹¹.

An additional patient population must also be considered: the extremely-low-birth weight (ELBW) neonate. These infants are defined as those weighing less than 1000g and appear to have several physiologic and pathologic factors that predispose them to excessive β -lactam accumulation in the CSF. Excessive accumulation of the β -lactam ring excites central nervous system neurons by blocking the synaptic activity of γ -butyric acid (GABA), which is an inhibitory neurotransmitter. The clearance of β -lactams (e.g., ampicillin) from the CSF seems to be dependent on an active transport mechanism in the choroid plexus, which is still immature and consequently can predispose them to seizures, even more so in the neonates < 750g.¹²

There are studies of ampicillin at the current clinical doses published in the medical literature, but the literature itself does not contain sufficient source data for review and labeling in neonates, especially for the preterm neonates. Data from pharmacokinetic studies are necessary to adequately label this drug for use in this population.

Types of studies: The requested two studies will occur sequentially. The protocol for Study 1 must be submitted to the FDA and must be agreed upon prior to initiation of Study 1. The results of Study 1 will be used to guide the dosing regimen(s) in Study 2; therefore the results of Study 1 must be submitted to the FDA and reviewed. If Study 1 does not identify two different dosing regimens of ampicillin for the neonates <750g, these infants will be enrolled directly into an open-label treatment arm and will receive a dose to be determined by Study 1.

Study 1: A dose-finding study to establish PK/PD parameters of ampicillin in the plasma and cerebrospinal fluid (CSF) following intravenous administration to term and pre-term neonates, for the treatment of suspected or confirmed sepsis and/or meningitis. The protocol should specify and justify a pharmacokinetic sampling plan during repeated dosing in neonates that receive ampicillin in combination with other antibiotics for the treatment of sepsis and/or meningitis. The dosing regimen provided will be doses of ampicillin that reflect the doses currently used in neonatology practice. The neonates will be stratified according to gestational and chronological age. Higher-body weight neonates (≥ 750 g for the group ≤ 34 weeks and ≥ 2000 g in the group > 34 weeks) within a gestational/chronological age group will be studied first, starting with a dose within the lower part of the recommended dose range. The lower-body weight neonates (<750g for the group ≤ 34 weeks and < 2000g in the group > 34 weeks) will also be studied in a sequential fashion. The protocol must specify and justify the starting dose for each of the 6 age subsets specified in Table 1. The analysis of the PK and safety data from the initial dose studied will guide the choice of dosing for the succeeding dose in Study 1. The results of this study should also provide data on the concentration of ampicillin in the CSF in at least 80% of the patients on treatment who are subjected to spinal taps as per standard of care.

The investigator will specify MIC₉₀ (minimum inhibitory concentration) of ampicillin for GBS, *L. monocytogenes*, and *E.coli*. These data can be determined either from recent available U.S. publications or data from recent isolates in the participating centers. In addition to MIC₉₀ being performed on all study isolates,

minimal bactericidal concentration (MBC) must be determined for GBS isolates from the study patients. The protocol should assure that MIC₉₀ and MBC determinations are validated and standardized, and that steps will be taken to minimize variability among centers.

Whenever a CSF sample is obtained, a blood sample to determine ampicillin level should be obtained concurrently. Also, the time and duration of the drug infusion must be recorded.

The protocol should define criteria for patients to be withdrawn from the study.

Note: The protocol for Study 2 must be submitted to the FDA and must be agreed upon prior to the initiation of Study 2. The results of Study 1 will provide the dosage regimens to be administered in Study 2.

Study 2: A prospective, randomized, double-blind, exploratory study comparing a low dose and high dose of ampicillin, determined after data from Study 1 have been submitted to and reviewed by the FDA, to evaluate the safety and tolerability of ampicillin in combination with other antibiotics in neonates with suspected or confirmed sepsis and/or meningitis. If Study 1 does not identify two different doses of ampicillin for the neonates <750g, these infants will be enrolled directly into an open-label treatment arm and will receive the dose guided by Study 1. Although the study will be powered for safety, efficacy data will also be obtained.

The safety endpoints must capture seizures, nephritis, hepatic, blood/lymphatic adverse events (AEs), plus any additional safety concerns identified in Study 1. All AEs must be reported.

The investigator will specify MIC₉₀ of ampicillin for GBS, L. monocytogenes, and E. coli. These data can be determined either from recent publications or data from recent isolates. In addition to MIC₉₀ being performed on all study isolates, MBC must be determined for GBS isolates from the study patients. The protocol should assure that MIC₉₀ and MBC determinations are validated and standardized, and that steps will be taken to minimize variability among centers.

The protocol should define criteria for patients to be withdrawn from the study. The protocol will address how patients with seizures are to be followed.

Objective/rationale:

Study 1: This study will obtain specific PK/PD parameters, as well as assess the safety and tolerability of ampicillin during repeated dosing, in combination with other antibiotics, for the treatment of sepsis and/or meningitis in neonates at specified gestational ages, chronological ages and birth weights.

Study 2: This study will have two objectives:

- (1) to obtain safety and tolerability information for the two different dosing regimens of ampicillin used in combination with other antibiotics to treat neonates with sepsis and/or meningitis. These dosing regimen(s) will be determined in Study 1. In the event that 2 dosing regimens for the neonates < 750g are not defined in Study 1, then the objective will be to assess the safety and tolerability of the optimal dosing regimen in patients < 750g;
- (2) to obtain population PK/PD information.

Age groups and number of patients to be studied:

Study 1: Term and pre-term neonates of both genders will be enrolled. All patients must have microbiological studies performed to confirm the diagnosis of sepsis and/or meningitis. The protocol should document the use of concomitant therapies.

If using traditional pharmacokinetic sampling methodology, there should be at least 6 neonates per dose level evaluated in each gestational and chronological age subgroups less than 34 weeks and at least 8 neonates in each chronological age group more than 34 weeks as displayed in Table 1 below. Data obtained from the gestational age group ≤ 28 weeks needs to be sufficient to guide dosing recommendations for the neonates < 750g and ≥ 750 g.

Table 1

Gestational Age	Chronological Age
≤ 28 weeks (N ≥ 24)	≤ 7 days (n ≥ 12)
	8-28 days (n ≥ 12)
$28 \leq 34$ weeks (N ≥ 24)	≤ 7 days (n ≥ 12)
	8-28 days (n ≥ 12)
> 34 weeks (N ≥ 32)	≤ 7 days (n ≥ 16)
	8-28 days (n ≥ 16)

If sparse sampling methods, i.e., population PK are employed, blood samples should be dispersed throughout the distribution and elimination phases of the drug concentration time profile to ensure proper parameter estimation and the protocol will need to specify and justify the number of patients to be studied. At least two blood samples should be obtained per neonate, preferably one taken at the end of the IV infusion and another one immediately prior to the start of IV infusion after repeated dosing.

When a spinal tap on therapy is performed as per standard of care, a CSF sample for ampicillin levels should be obtained in at least 80% of the patients. To the extent possible, additional CSF samples from other patients should also be

obtained. The time of the CSF sampling in relation to the time of the last ampicillin dose administered must be recorded. Whenever a CSF sample is obtained, a blood sample for ampicillin level should be obtained concurrently.

All the neonates in this study must be assessed for renal function at screening (urinary output and laboratory assessment as specified on page 7). Patients with impaired renal function may be included and evaluated as a subset.

Study 2: Term and pre-term neonates of both genders will be enrolled. All patients must have microbiological studies performed to confirm the diagnosis of sepsis and/or meningitis. The protocol should document the use of concomitant therapies.

Patients to be enrolled in Study 2 will be stratified by gestational age as requested in Study 1 (see table 1). The protocol must specify and justify the minimum number of patients to be enrolled such that the study is powered to identify adverse events occurring in at least 1% of the patients exposed to the study drug. All chronological age groups within each gestational age must be adequately represented.

In the event that Study 1 does not identify two different dosing regimens for the population <750g, such neonates who are evaluable from the safety perspective will be enrolled in an open-label treatment arm, as a subset of the patients ≤ 28 weeks gestational age. These <750g neonates will receive the dosing regimen identified in Study 1. Neonates <750 g also need to be represented as a subset of the gestational age group ≤ 28 weeks and enough evaluable patients will be enrolled to provide needed safety information.

Inclusion Criteria:

Studies 1 and 2 will include male and female neonates with either suspected or confirmed infection. The protocol will specify additional criteria for study inclusion and exclusion.

Study Endpoints:

Study 1: Determination of relevant pharmacokinetic parameters so that appropriate dosing recommendations for the intravenous administration of ampicillin for the treatment of neonatal sepsis and/or meningitis can be made, as well as assessment of safety and tolerability. Plasma clearance and volume of distribution of ampicillin will be calculated and other PK parameters such as the maximum plasma concentration at the end of the IV infusion (C_{\max}), time of C_{\max} (T_{\max}), area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}), the elimination rate constant (K_e), terminal elimination half-life ($t_{1/2}$), and AUC extrapolated to infinity ($AUC_{0-\infty}$) will be determined. The PK/PD parameters (e.g., $T > MIC_{90}$ for each of the microorganisms of interest- *E. coli*, *L. monocytogenes*, GBS), CSF penetration and CSF PK parameters will be determined to the extent possible. The time of the CSF sampling in relation to the time of the last ampicillin dose administered must be recorded. If a sparse sampling method, (i.e., population PK) is employed, blood samples should be

dispersed throughout the distribution and elimination phases of the drug concentration time profile to ensure proper parameter estimation and the protocol will need to specify and justify the number of patients for the study. Whenever a CSF sample is obtained, a blood sample to determine ampicillin level should be obtained simultaneously.

The protocol should include a description of the methodology to be used for measuring ampicillin concentration in the blood and CSF samples obtained. The methodology must be validated. Tests must be performed on microliter serum samples, to the extent possible. Bio-analytical methods to determine ampicillin concentrations must be capable of evaluating the smallest possible sample volumes (preferably less than 100 microliters).

The MIC₉₀ will be obtained for all isolated organisms and in addition, MBC for GBS isolates.

The evaluation of safety and tolerability will include a physical examination and clinical laboratory assessment before, during, and at the end of the treatment. The protocol will specify monitoring procedures for adverse events. Laboratory tests must include, but are not limited to, complete blood counts (CBC), blood culture, electrolytes, blood urea nitrogen (BUN) and creatinine levels. The protocol must specify and justify the number of samples and the maximum amount of blood to be drawn for study purposes (including PK, blood culture, and safety labs) and this amount must be approved by the IRB.

In addition, safety assessments will include occurrence of any adverse events (AEs) including but not limited to seizures, intraventricular hemorrhage, superinfections (particularly fungal infections), vital signs that include heart rate (HR), blood pressure (BP), respiratory rate (RR), pulse oximetry, apnea monitoring, standard laboratory assessments of hematologic, liver and renal function, and growth (weight, length, and head circumference). AEs will be followed to their resolution or stabilization. Criteria for identification and clinical evaluation of suspected seizures will be described in the protocol.

Study 2: The evaluation of safety and tolerability will include a physical examination and clinical laboratory assessment before, during, and at the end of the treatment. The protocol will specify monitoring procedures for adverse events. Laboratory tests must include, but are not limited to, complete blood counts (CBC), blood culture, electrolytes, blood urea nitrogen (BUN) and creatinine levels. The protocol should specify the methodology for measuring ampicillin concentration on the blood samples obtained. The methodology must be validated. Tests must be performed on microliter serum samples, to the extent possible. Bio-analytical methods to determine ampicillin concentrations must be capable of evaluating the smallest possible sample volumes (preferably less than 100 microliters). The protocol must specify and justify the number of samples and the maximum amount of blood to be drawn for study purposes (including PK, blood culture, and safety labs) and this amount must be approved by the IRB.

In addition, safety assessments will include occurrence of any adverse events (AEs) including but not limited to seizures, intraventricular hemorrhage, superinfections (particularly fungal infections), vital signs that include heart rate (HR), blood pressure (BP), respiratory rate (RR), pulse oximetry, apnea monitoring, standard laboratory assessments of hematologic, liver and renal function, and growth (weight, length, and head circumference). AEs will be followed to their resolution or stabilization. Criteria for identification and clinical evaluation of suspected seizures will be described in the protocol.

The MIC₉₀ will be obtained for all isolated organisms and in addition, MBC for GBS isolates.

Additional study endpoints may be added based on the results of Study 1.

Data Monitoring Committee (DMC):

Both Study 1 and Study 2 must include a DMC with pertinent expertise to provide ongoing oversight of trial data regarding the continuing safety of patients as well as the continuing validity and scientific merit of the studies. The charter of the committee should include guidelines for monitoring. The operating plan for the DMC should be submitted to the Division for review and comment.

Drug Specific Safety Concerns:

Ampicillin is excreted by the kidneys. Patients must have renal function monitored due to concerns regarding ampicillin accumulation secondary to renal immaturity. The ELBW neonates (especially those with body weight less than 750g) may be at greater risk for seizures, since excessive β -lactam accumulation, which can be epileptogenic, may occur in this unique patient population¹. The protocol should specify how the neonates will be monitored for seizures and renal function abnormalities.

The clinical manifestation of seizures in newborn and young infants can be subtle. The protocol must specify the definition of seizures and the criteria for identification and documentation of possible seizures and must address the role of electroencephalograms and other diagnostic methods in seizure diagnosis. Collection of a serum ampicillin level at time of suspected seizure is strongly encouraged.

Other reported AEs related to ampicillin include: hepatic, hematologic, anaphylaxis and interstitial nephritis.

General Safety Concerns:

Each protocol must specify the maximum amount of blood to be drawn for study purposes (including PK, blood culture, and safety labs) and this amount must be approved by the IRB.

The protocols should address hearing assessments in patients with documented meningitis.

For patients on aminoglycosides, drug levels must be obtained for monitoring purposes.

Drug Information:

- **Route of administration:** Intravenous. In Study 1, the protocol should specify the time over which the dose is to be administered, as well as the diluent to be used and the maximum concentration for the IV solution. The ampicillin infusion rate should be standardized and documented for each patient.
- **Doses:** The following dosing regimens of ampicillin reflect current literature and clinical practice. The protocol must specify and justify the starting dose for each break-out group as specified in Table 1.
 - Infants under 32 weeks:
 - 0- 4 weeks of age: BW \leq 750g: 50¹²-200 mg/kg/day, divided q 12h
BW > 750g: 100-200 mg/kg/day, divided q 12h
 - Infants 32-36 weeks:
 - \leq 1 week of age: BW \leq 2000g: 100-200 mg/kg/day, divided q 12h
BW > 2000g: 150-200 mg/kg/day, divided q 8-12h
 - > 1 week of age: BW \leq 2000g: 150-300 mg/kg/day, divided q 8h
BW > 2000g: 200-300 mg/kg/day, divided q 6-8h
 - Infants > 36 weeks:
 - \leq 1 week of age: BW \leq 2000g, 100-300 mg/kg, divided q 8-12h
BW > 2000g, 150-300 mg/kg, divided q 8- 12h
 - > 1 week of age: BW \leq 2000g, 150-300 mg/kg, divided q 6- 8h
BW > 2000g, 200-300 mg/kg, divided q 6-8h

After evaluation of the data resulting from Study 1, dosing regimen(s) will be selected for Study 2.

- **Formulation:** commercially available IV solution

Statistical information (statistical analyses of the data to be performed):

Study 1: Appropriate statistical analysis of the PK and PK/PD should be performed and descriptive summary of results (including comparison of 90% confidence intervals of parameters obtained from the various subgroups) should be provided. The effect of other intrinsic co-variates and extrinsic co-variates (concomitant medications) on ampicillin pharmacokinetics in these neonates should also be explored.

Study 2: This is an exploratory study that must enroll an adequate number of patients to demonstrate the safety and tolerability of ampicillin at the specified dosing regimen(s). A sufficient number of patients, who are evaluable from the safety perspective, will be enrolled as needed to identify adverse events occurring in at least 1% of the patients exposed to the study drug. Descriptive subgroup analyses must be performed to include sex, birth weight, and gestational age subgroups. Since steroids decrease the penetration of antibiotics in the CSF, the patients using such therapy should be analyzed as a subset. This study is to be powered for safety; efficacy data will also be collected.

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of these studies.

Format of reports to be submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before December 31, 2009. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission “**PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST**” in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission “**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission “**SUBMISSION OF PEDIATRIC STUDY REPORTS - COMPLETE RESPONSE TO WRITTEN REQUEST**” in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of

supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked “**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

If you have any questions, call *Susmita Samanta*, Regulatory Health Project Manager, at phone 301-827-2128.

Sincerely,

{See appended electronic signature page}

OFFICE DIRECTOR

Director

Office of Drug Evaluation XX, HFD-###
Center for Drug Evaluation and Research

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- ² Stoll BJ, Gordon T, Korones SB, et al. Early-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. *J Pediatr* 1996; 129:72-80.
- ³ Byington CL, Rittichier KK, Bassett KE, et al. Serious Bacterial Infections in Febrile Infants Younger Than 90 Days of Age: The Importance of Ampicillin-Resistant Pathogens. *Pediatrics* 2003; 111(5): 964-968.
- ⁴ Sadow KB, Derr R, Teach SJ. Bacterial Infections in Infants 60 Days and Younger. *Arch Pediatr Adolesc Med* 1999; 153: 611-614.
- ⁵ Stoll BJ, Hansen N, Fanaroff AA, et al. Changes in Pathogens Causing Early-Onset Sepsis In Very-Low-Birth-Weight Infants. *N Engl J of Med* 2000; 347(4): 240-247.
- ⁶ Klein JO. Current antibacterial therapy for neonatal sepsis and meningitis. *Pediatr Infect Dis J* 1990; 9(10):783-784.
- ⁷ Schauf V, Deveikis A, Riff L, et al. Antibiotic-killing kinetics of Group B streptococci. *J Pediatr* 1976; 89:194-8.
- ⁸ Deveikis A, Schauf V, Mizen M, et al. Antimicrobial therapy of experimental Group B streptococcal infection in mice. *Antimicrob Agents Chemother* 1977; 11:817-820
- ⁹ American Academy of Pediatrics. Group B streptococcal infections. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26 ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:584-591.
- ¹⁰ American Academy of Pediatrics. Group B streptococcal infections. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26 ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003: 701.
- ¹¹ McCracken GH and Nelson JD. Antimicrobial Therapy for Newborns. Practical Application of Pharmacology to Clinical Usage. Grune & Stratton, New York, NY, 1977.
- ¹² Shaffer CL, Davey AM, Ransom JL, et al. Ampicillin –Induced Neurotoxicity in Very-Low-Birth-Weight Neonates. *Ann Pharmacoth* 1998; 32: 482-484